MERCK & CO INC *WO 200236734-A2

2000.10.12 2000-239732P(+2000US-239732P) *(2002.05.10)* C12N

New aza- and polyaza-naphthalenyl ketones useful in the treatment of e.g. infection by HIV (Eng)

C2002-169132 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW)

Addnl. Data: ZHUANG L, WALJ S, PAYNE L S, YOUNG S D, FISHER T E, EMBREY M, GUARE J P
2001.10.09 2001WO-US42553

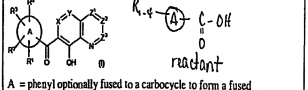
B(6-H, 11-C1C, 11-C7, 12-K4, 14-A2B1, 14-G1B, 14-L6) .7

NOVELTY

Aza- and polyaza-naphthalenyl ketones or their salts are new.

DETAILED DESCRIPTION

Aza- and polyaza-naphthalenyl ketones of formula (I) or their salts are new.



A = phenyl optionally fused to a carbocycle to form a fused carbocyclic ring, or a heterocycle containing at least one heteroatom selected from N, O, or S and balance of carbon atoms, with at least one of the ring atom being carbon (all optionally substituted by R^1 - R^4);

X = N or C-Q^1;

Y = N or C-Q^2;

Z^1 = N or C-Q^3;

Z^2 = N or C-Q^4;

Z^3 = N or CH;

Q^1 - Q^4 = T, T', H, 2-5C alkynyl, 2-5C alkynyl-$CH_2N(R_a)_2$, 2-5C alkynyl-$CH_2N(OR_a)$, -$N(R_b)$-$C(NR_a)$-$N(R_a)_2$ or 1-6C (fluoro)alkyl substituted with R_k, -O-(1-4C)alkyl-R_k, -$N(R_b)$-R_k, -$N(R_b)$(1-6C)alkyl substituted with 1 or 2 R_k, -$N(R_b)$(1-6C)alkyl-OR_b, -C(=O)N(1-6C)alkyl-R_k, or (2-5C)alkynyl-$CH_2S(O)_n$-R_a;

T = 1-6C alkyl, 1-6C fluoroalkyl, OH, -O(1-6C)alkyl, O-(1-6C)fluoroalkyl, halo, CN;

T' = 1-6C alkyl-O(R_a), 0-6C alkyl-C(=O)R_a, 0-6C alkyl-CO_2R_a, 0-6C alkyl-S(R_a), -$N(R_a)_2$, 1-6C alkyl-$N(R_a)_2$, 0-6C alkyl-C(=O)$N(R_a)_2$, 1-6C alkyl-$N(R_a)C(R_a)$=O, -SO_2R_a, -$N(R_a)SO_2R_a$, -$N(R_a)$-(1-6C)alkyl-$N(R_a)_2$, -$N(R_a)$(1-6C)alkyl-$N(R_a)$-$C(R_a)$=O, -R_k, -$N(R_a)$-(1-6C)alkyl-SR_k, -$N(R_a)$(1-6C)alkyl-OR_a, 2-5C alkenyl-R_k, 2-5C alkynyl-R_k, -O-R_k, -O-(1-4C)alkyl R_k, -S(O)$_n$-R_k, -S(O)$_n$(1-4C)alkyl-R_k, -O(1-6C)alkyl-OR_k, -O-(1-6C)alkyl-O(1-4C)alkyl-R_k, -O(1-6C)alkyl-SR_k;

R^1 and R^2 = T, T' H, -NO_2, (2-5C)alkenyl, O(1-6C)-OR_a, -O(1-6C)alkyl-SR_a, O(1-6C)alkyl-$NH\text{-}CO_2\text{-}(R_a)$, -O(2-6C)alkyl-$N(R_a)_2$ or 1-6C (fluoro)alkyl mono- or di-substituted with 1 or 2 R_k, -O-(1-4C)alkyl-R_k, -O-(1-6C)alkyl(OR_a)R_k, 1-6C alkyl (OR_a)(1-4C alkyl-R_k), 0-6C alkyl-$N(R_b)$(1-4C alkyl-R_k), 0-6C alkyl S(O)$_n$-R_k, 1-6C alkyl-S(O)$_n$(1-4C)alkyl-R_k, (0-6C)alkyl-C(O)-R_k or 0-6C alkyl-C(O)-(1-4C)alkyl-R_k;

R_3 and R_4 = T, H, -NO_2, (1-6C)alkyl-OR_a, (0-6)alkyl-C(=O)R_a, (0-6C)alkyl-CO-2R_a, (0-6C)alkyl-SR_a, -$N(R_a)_2$, 1-6C alkyl-$N(R_a)_2$, 0-6C alkyl-C(=O)$N(R_a)_2$, -$SO_2(R_a)$, -$N(R_a)SO_2(R_a)$, 2-5C alkenyl, O(1-6C)alkyl-OR_a, O(1-6C)alkyl-S(R_a), O(1-6C)alkyl-$NH\text{-}CO_2R_a$, O(2-6C)alkyl-$N(R_a)_2$ or oxo;

R_a = H or 1-6C (fluoro)alkyl;

R_b = H, 1-4C (fluoro)alkyl, -R_k, 2-3C alkenyl, 1-4C alkyl-R_k, 2-3C alkenyl-R_k, -S(O)$_n$-R_k, or -C(O)-R_a;

R_c = H, 1-6C alkyl, 1-6C alkyl substituted with -$N(R_a)_2$, or 1-4C alkyl-aryl (aryl is optionally mono- to penta-substituted by T, or -S(1-6C)alkyl);

R_k = carbocycle or heterocycle (optionally mono- to penta-substituted by T, -S-(1-6C)alkyl, oxo, -$(CH_2)_{0.3}$-C(=O)$N(R_a)_2$, -$(CH_2)_{0.3}$-C(=O)-R_a, -$N(R_b)$-C(=O)OR_a, -$N(R_a)$-C(=O)OR_a, -$(CH_2)_{1.3}N(R_a)$-C(=O)-R_a, aryl, aryloxy, (1-4C)alkyl substituted with aryl, heteromonocycle, (1-4C)alkyl substituted with a heteromonocycle, heteromonocyclylcarbonyl-(0-6C)alkyl, N-heteromonocyclyl-N(1-6C)alkyl-amino-)(where aryl, aryloxy, (1-4C)alkyl substituted by aryl (optionally substituted by halo,

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alkynyl-$CH_2N(OR_a)$, -$N(R_b)$-$C(NR_a)$-$N(R_a)_2$ or 1-6C (fluoro)alkyl substituted with R_k, -O-(1-4C)alkyl-R_k, -$N(R_b)$-R_k, -$N(R_b)$(1-6C)alkyl substituted with 1 or 2 R_k, -$N(R_b)$(1-6C)alkyl-OR_b, -C(=O)N(1-6C)alkyl-R_k, or (2-5C)alkynyl-$CH_2S(O)_n$-R_a;

T = 1-6C alkyl, 1-6C fluoroalkyl, OH, -O(1-6C)alkyl, O-(1-6C)fluoroalkyl, halo, CN;

T' = 1-6C alkyl-O(R_a), 0-6C alkyl-C(=O)R_a, 0-6C alkyl-CO_2R_a, 0-6C alkyl-S(R_a), -$N(R_a)_2$, 1-6C alkyl-$N(R_a)_2$, 0-6C alkyl-C(=O)$N(R_a)_2$, 1-6C alkyl-$N(R_a)C(R_a)$=O, -SO_2R_a, -$N(R_a)SO_2R_a$, -$N(R_a)$-(1-6C)alkyl-$N(R_a)_2$, -$N(R_a)$(1-6C)alkyl-$N(R_a)$-$C(R_a)$=O, -R_k, -$N(R_a)$-(1-6C)alkyl-SR_k, -$N(R_a)$(1-6C)alkyl-OR_a, 2-5C alkenyl-R_k, 2-5C alkynyl-R_k, -O-R_k, -O-(1-4C)alkyl R_k, -S(O)$_n$-R_k, -S(O)$_n$(1-4C)alkyl-R_k, -O(1-6C)alkyl-OR_k, -O-(1-6C)alkyl-O(1-4C)alkyl-R_k, -O(1-6C)alkyl-SR_k;

R^1 and R^2 = T, T' H, -NO_2, (2-5C)alkenyl, O(1-6C)-OR_a, -O(1-6C)alkyl-SR_a, O(1-6C)alkyl-$NH\text{-}CO_2\text{-}(R_a)$, -O(2-6C)alkyl-$N(R_a)_2$ or 1-6C (fluoro)alkyl mono- or di-substituted with 1 or 2 R_k, -O-(1-4C)alkyl-R_k, -O-(1-6C)alkyl(OR_a)R_k, 1-6C alkyl (OR_a)(1-4C alkyl-R_k), 0-6C alkyl-$N(R_b)$(1-4C alkyl-R_k), 0-6C alkyl S(O)$_n$-R_k, 1-6C alkyl-S(O)$_n$(1-4C)alkyl-R_k, (0-6C)alkyl-C(O)-R_k or 0-6C alkyl-C(O)-(1-4C)alkyl-R_k;

R_3 and R_4 = T, H, -NO_2, (1-6C)alkyl-OR_a, (0-6)alkyl-C(=O)R_a, (0-6C)alkyl-CO-2R_a, (0-6C)alkyl-SR_a, -$N(R_a)_2$, 1-6C alkyl-$N(R_a)_2$, 0-6C alkyl-C(=O)$N(R_a)_2$, -$SO_2(R_a)$, -$N(R_a)SO_2(R_a)$, 2-5C alkenyl, O(1-6C)alkyl-OR_a, O(1-6C)alkyl-S(R_a), O(1-6C)alkyl-$NH\text{-}CO_2R_a$, O(2-6C)alkyl-$N(R_a)_2$ or oxo;

R_a = H or 1-6C (fluoro)alkyl;

R_b = H, 1-4C (fluoro)alkyl, -R_k, 2-3C alkenyl, 1-4C alkyl-R_k, 2-3C alkenyl-R_k, -S(O)$_n$-R_k, or -C(O)-R_a;

R_c = H, 1-6C alkyl, 1-6C alkyl substituted with -$N(R_a)_2$, or 1-4C alkyl-aryl (aryl is optionally mono- to penta-substituted by T, or -S(1-6C)alkyl);

R_k = carbocycle or heterocycle (optionally mono- to penta-substituted by T, -S-(1-6C)alkyl, oxo, -$(CH_2)_{0.3}$-C(=O)$N(R_a)_2$, -$(CH_2)_{0.3}$-C(=O)-R_a, -$N(R_b)$-C(=O)OR_a, -$N(R_a)$-C(=O)OR_a, -$(CH_2)_{1.3}N(R_a)$-C(=O)-R_a, aryl, aryloxy, (1-4C)alkyl substituted with aryl, heteromonocycle, (1-4C)alkyl substituted with a heteromonocycle, heteromonocyclylcarbonyl-(0-6C)alkyl, N-heteromonocyclyl-N(1-6C)alkyl-amino-)(where aryl, aryloxy, (1-4C)alkyl substituted by aryl (optionally substituted by halo,

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(1-6C)alkyl, -O-(1-6C)alkyl, (1-6C)alkyl substituted by $N(R_a)_2$, 1-6C fluoroalkyl or -OH) and heteromonocycle, (1-4C)alkyl substituted by a heteromonocycle, heteromonocyclyl-carbonyl(0-6C)alkyl, N-heteromonocyclyl-N-(1-6C)alkyl-amino(optionally substituted by mono- to tri-halo, 1-6C alkyl, -O-(1-6C)alkyl, 1-6C fluoroalkyl, oxo or OH));

n = 0 - 2.

Provided that:

(1) X and Y are not both N;

(2) when A is phenyl, or X, Y and Z^1 - Z^3 is CH, then at least one of R^1 - R^4 is not H;

(3) when A is phenyl, X is CH, Y is CQ^2 (where Q^2 is halo, 1-6C alkyl or phenyl optionally substituted by halo, 1-6C alkyl or benzyl (optionally substituted by halo, or 1-6C alkyl)), Z^1 - Z^3 is CH, and one of R^1 - R^4 is H, halo, or 1-6C alkyl, then the other of R^1 - R^4 is not H, halo, or 1-6C alkyl;

(4) when A is phenyl, or X, Y and Z^1 - Z^3 is CH, then at least one of R^1 - R^4 is not H; and

(5) when A is phenyl, X is CH, Y is CH, Z^1 is CQ^3, Z^2 and Z^3 is CH, then either Q^3 is not substituted by benzyl or at least one of R^1 - R^4 is not H.

ACTIVITY

Anti-HIV; Virucide.

MECHANISM OF ACTION

HIV integrase and HIV replication inhibitors.

USE

In the treatment or prevention of infection by HIV; treating, preventing or delaying onset of AIDS (claimed) or AIDS related complications (ARC). The compounds are also useful in the preparation and execution of screening assay for antiviral compounds; for isolating enzyme mutants; and in establishing or determining the binding site of other antiviral to HIV integrase e.g. by competitive inhibition.

ADVANTAGE

The compounds have highly specific inhibition capacity of HIV

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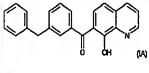
(con't)

integrase and HIV replication.

SPECIFIC COMPOUNDS

25 compounds are specifically claimed as (I) e.g. 1-(3-benzylphenyl)-1-(8-hydroxyquinolin-7-yl)methanone (1A)



(1A)

ADMINISTRATION

The compounds are administered orally, parenterally (including subcutaneous injection, intravenous, intramuscular, intrasternal injection, or infusion). Dosage is from 0.1 - 1000 (especially 0.5 - 100) mg/kg body weight in divided form.

EXAMPLE

A septum was added to tert-butylamine (7.24 ml) in toluene (50 ml). The reaction was cooled to 78°C and bromine (1.69 ml) was added, stirred for 10 minutes followed by addition of 8-hydroxyquinoline (5 g) in chloroform (10 ml). The addition mixture was stirred for 1 hour, warmed to ambient temperature, diluted with ethyl acetate (200 ml) and extracted. The organic extracts were dried, filtered and purified to give 7-bromoquinolin-8-ol (A). (A) (3.1 g), diisopropylethylamine (7.23 ml) and methyl chloride (100 m) were added. MEM chloride (1.90 ml) was added and the reaction was stirred for 18 hours. After which another MEM chloride (0.95 ml) was added. This mixture was stirred for 1 hour, water (50 ml) was added and the organic solvent removed in vacuum. The residue was extracted, washed dried and filtered to give 7-bromo-8- (2-methoxy-ethoxymethoxy)-quinoline (B). (B) (0.765 g) and tetrahydrofuran (THF) (10 ml) were added in flask. The flask was cooled to -78°C and to it was added t-butyllithium (3.6 ml of a 1.5M solution in pentane, 5.4 mmol). The reaction was stirred for 15 minutes then N-methyl-N-methoxy-(3-benzyl)benzenecarboxyamide (0.626 g) THF (5 ml) was added at 74°C. This mixture was stirred for 5 minutes, warmed to ambient temperature and the reaction was quenched by the addition of saturated aqueous NH_4Cl. The solution was extracted, washed, dried and filtered to give 1-(3-benzylphenyl)[8-[(2-methoxyethoxy)methoxy]quinolin-7-yl]methanone (C). (C) (0.2 g), MeOH (3 ml) and trifluoroacetic acid (1.081 ml) were added and the

reaction was stirred for 3 days, after which time it was poured into aqueous saturated $NaHCO_3$ (20 ml) and extracted, dried, filtered and purified to give 1-(3-benzylphenyl)-1-(8-hydroxyquinolin-7-yl)methanone.

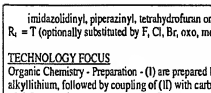
DEFINITIONS

Preferred Definitions:

X = N;
Y = C-Q^2;
Z^1 = C-Q^1;
Z^2 = C-Q^2;
Z^3 = CH;
Q^1 and Q^2 = H;
R^1 = -R_5, $(CH_2)_{1-4}$-R_6, -OR$_6$, or -O-$(CH_2)_{1-4}$-R_6;
R^2 = H, methyl, ethyl, CF_3, methoxy, ethoxy, -OCF_3, F, Cl, Br, -CN, -CH_2OR_4, -CO_2R_6, -SR_6, -$N(R_6)_2$, -$(CH_2)_{1-3}N(R_6)_2$, -SO_2R_6, -$(CH_2)_{1-4}$-N(-R_6)-C(=R_7)=O, -R_6, -$(CH_2)_{1-4}R_6$, -OR$_6$ or -O-$(CH_2)_{1-4}R_6$;
R'_1 = S^1, S^2, S^3 or S^4;
S^1 = phenyl (optionally mono- to tetra-substituted by T^1, -S-CH_3, phenyloxy (optionally mono- to tri-substituted by halo, methyl, -CF_3, OH), -$N(R_6)_2$, -$(CH_2)_{1-3}N(R_6)_2$, -$(CH_2)_{1-3}N(R_6)_2$, -R_6, -$(CH_2)_{0-3}C(=O)N(R_6)_2$ or -$(CH_2)_{0-3}C(=O)R_6$;
T^1 = F, Cl, Br, methyl, -CF_3, methoxy, OCF_3, phenyl, OH or CN;
S^2 = 3-6C cycloalkyl (optionally mono- to tri-substituted by T^1);
S^3 = 5 or 6 membered ring selected from thienyl, pyridyl, imidazolyl, pyrrolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isooxazolyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl, furanyl or pyridazinyl (optionally substituted on N or C by mono or di T^1, -S(1-6C)alkyl, phenyloxy (optionally substituted by F, Cl, Br, methyl, -CF_3, or OH), -$N(R_6)_2$, 1-6C alkyl-$N(R_6)_2$, -R_6, oxa, -$(CH_2)_{0-3}C(=O)N(R_6)_2$ or -$(CH_2)_{0-3}C(=O)R_6$;
S^4 = 5 - 6 membered T (optionally mono- or di-substituted by T^1, =O, benzyl, phenylethyl, -$(CH_2)_{0-3}$-C(=O)$N(R_6)_2$, -$(CH_2)_{0-3}C(=O)R_6$, $N(R_6)$-C(=O)R_6, $N(R_6)$-C(=O)OR$_6$, $N(R_6)$-C(=O)$OC(CH_3)_3$, $(CH_2)_{0-3}N(R_6)$-C(=O)R_6, $N(R_6)_2$, $(CH_2)_{1-3}N(R_6)_2$, $(CH_2)_{0-3}C(=O)R_6$, -R_6, -$N(R_6)R_6$ or $(CH_2)_{1-3}R_6$);
T = piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isooxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuran or pyrazolidinyl
R_6 = T (optionally substituted by F, Cl, Br, oxo, methyl or methoxy).

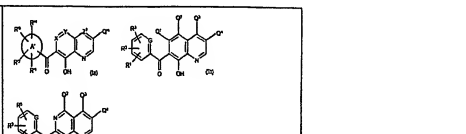
TECHNOLOGY FOCUS

Organic Chemistry - Preparation - (I) are prepared by treating (II) with alkyllithium, followed by coupling of (II) with carboxylic derivative of (III) to provide ketone of formula (I).



(II) (III)

G^1 = alkyl;
Hal = halogen; and
G^2 = OH, alkoxy, halide, NMe(OMe).
Preferred Compound: The ketones are of formula (Ia) (preferably (Ib), especially (Ic)).



(IA) (IB) (IC) (ID)

A^1 = phenyl, a fused carbocyclic ring selected from indan, 1-H indene, naphthalene, 1,2-dihydro-naphthalene, 1,2,3,4-tetrahydro-naphthalene, 6,7,8,9-tetrahydro-5H-benzocycloheptene, 6,7-dihydro-5H-benzocycloheptene, 9H-fluorene, anthracene, or 9,10-Dihydro-anthracene, 5- or 6-membered optionally saturated monocyclic heterocycle containing 1 - 4 N atoms, or 0 - 2 O or S atoms with at least one of the ring atoms being carbon (all optionally substituted by R^1 - R^4);
Q^{*1} = H or 1-4C alkyl;
Q^{*2} = T_1, T_2, 2-3C alkynyl, -C equivalent to C-$CH_2N(R_6)_2$, -C

(con't)

equivalent to C-CH_2OR_a, -$N(R_c)$-R_b, -$N(R_c)$(1-4C)alkyl substituted with 1 or 2 R_b, -$N(R_c)$(1-4C)alkyl-OR_b, -C(=O)N(1-4C)alkyl-R_b, -C equivalent to C-CH_2SR_a, or -C equivalent to C-$CH_2SO_2R_a$;

T_1 = H, 1-4C (fluoro)alkyl, -O-1-4C (fluoro)alkyl or CN;

T_2 = OH, halo, -1-4C alkyl-OR_a, -$(CH_2)_{0-3}C(=O)R_a$, -$(CH_2)_{0-2}CO_2$-R_a, -$N(R_a)_2$, 1-4C alkyl-$N(R_a)_2$, -$(CH_2)_{0-2}C(=O)N(R_a)_2$, (1-4C)alkyl-$N(R_a)$-$C(R_c)$=O, -$SO_2$-$R_a$, -$N(R_a)SO_2R_a$, -$N(R_a)$(1-4C)alkyl-$SR_a$, -$N(R_a)$(1-4C)alkyl-$OR_a$, -$N(R_a)$(1-4C)alkyl-$N(R_a)_2$, $N(R_a)$(1-4C)alkyl-$N(R_a)$-$C(R_c)$=O, -R_b, 1-4C (fluorn)alkyl mono or di substituted with R_b, -$S(O)_nR_b$;

Q^3 = T_1, F, Cl, or Br, (1-4C)alkyl-OR_a or (1-4C)alkyl substituted R_b;

Q^4 = T_1, F, Cl, or Br, 1-6C alkyl-OR_a, -$N(R_a)_2$, or (1-6C)alkyl-$N(R_a)_2$;

R^1 and R^2 = T_1, T_2, -O-(1-4C)alkyl-OR_a, -O(1-4C)alkyl-SR_a, -O(1-4C)alkyl-NH-CO_2R_a, -O-(2-4C)alkyl-$N(R_a)_2$, -$S(O)_n$(1-4C)alkyl-R_b, -O-(1-4C)alkyl-R_b, -O-(1-4C)alkyl-O-(1-4C)alkyl-R_b, -O(1-4C)alkyl-SR_b, or (0-4C)alkyl-$N(R_b)(R_c)$;

R^{13} and R^{14} = T_1, halo, -OH, 1-4C alkyl-OR_a, -O-(1-4C)alkyl-OR_a, -O-(1-4C)alkyl-SR_a, -O-(1-4C)alkyl-NH-CO_2R_a, or -O-(2-4C)alkyl-$N(R_a)_2$;

R^*_a = H, 1-4C alkyl;

R^*_b = H, 1-4C (fluoro)alkyl, -R_a, (1-4C)alkyl-R_b, -$S(O)_nR_b$, or -C(=O)R_a;

R^*_c = H, 1-4C alkyl optionally substituted with -$N(R_a)_2$, or 1-4C alkyl-phenyl (phenyl is optionally mono- to tri-substituted by halo, 1-4C (fluoro)alkyl, -O(1-4C)(fluoro)alkyl, CN, OH or -S-(1-4C)alkyl);

R^*_k = P^1, P^2, P^3, P^4, P^5, or P^6;

P^1 = T or T_4;

T_4 = -S-(1-6C)alkyl, phenyloxy (optionally mono- to tri-substituted by halo, 1-6C (fluoro)alkyl or OH), -$N(R_a)_2$, 1-6C alkyl-$N(R_a)_2$, -R_a, -$(CH_2)_{0-3}C(=O)N(R_a)_2$, or $(CH_2)_{0-3}C(=O)R_a$;

P^2 = 3-7C cycloalkyl optionally mono- to tri-substituted by T or phenyl;

P^3 = 3-7C cycloalkyl fused with a phenyl ring optionally mono - penta substituted by T;

P^4 = 5 or 6 membered heteroaromatic ring (optionally substituted by T or T_4) containing 1 - 4 heteroatoms O, N, or S;

P^5 = 5 or 6 membered saturated heterocyclic ring (optionally substituted by T, oxo, phenyl, benzyl, phenylethyl, -$(CH_2)_{0-3}C(=O)N(R_a)_2$, -$(CH_2)_{0-3}$-$C(=O)N(R_a)_2$, $N(R_a)$-$C(=O)R_a$, $N(R_a)$-$C(=O)OR_a$, -$(CH_2)_{1-3}N(R_a)$-$C(=O)R_a$, -$N(R_a)_2$, -$(CH_2)_{1-3}N(R_a)_2$, R_a, -$N(R_a)R_a$ or $(CH_2)_{1-3}R_i$) containing 1 - 4 heteroatoms;

P^6 = 8 - 10 membered heteroaromatic ring (optionally substituted by T or =O) containing 1 - 4 heteroatoms O, N, or S;

R_i = 5 or 6 membered optionally saturated heteromonocyclic ring (optionally substituted by halo, oxo, 1-4C alkyl or -O(1-4C)alkyl) containing 1 - 4 N, or naphthyl;

G = N or CH optionally substituted by one of R^1 - R^3.

Provided that:

(1) when G is not N and Q^1 - Q^4 = H, then at least one of R^1 - R^3 is not H;

(2) when G is not N, Q^1 is H, Q^2 is halo or 1-6C alkyl or phenyl (optionally substituted by halo or 1-6C alkyl), or benzyl (optionally substituted by halo or 1-6C alkyl), Q^3 and Q^4 is H and one of R^1 - R^3 is H, halo or 1-6C alkyl, then R^1 - R^3 is not H, halo, or 1-6C alkyl;

(3) when G is not N, Q^1 - Q^4 is H and one of R^1 - R^3 is -CO_2R_a, then at least one of R^1 - R^2 is not H; and

(4) when G is not N and Q^1 - Q^4 is H, then either Q^3 is not substituted by benzyl or at least one of R^1 - R^3 is not H.

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